THIS OPINION WAS NOT WRITTEN FOR PUBLICATION

The opinion in support of the decision being entered today (1) was not written for publication in a law journal and (2) is not binding precedent of the Board.

Paper No. 30

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

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Ex parte PETER S. MEZES,
RUTH A RICHARD, JOSEPH A. AFFHOLTER
and NICOLAS J. KOTITE

_____

Appeal No. 1996-2013
Application 07/935,695

_____

ON BRIEF

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Before WINTERS, ROBINSON and SCHEINER, Administrative Patent Judges.

SCHEINER, Administrative Patent Judge.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 from the final rejection of claims 1, 3, 4, 8 through 18, 21 and 23 through 25. Claims 19 and 20, the only other claims remaining in the application, have been withdrawn from consideration by the examiner.

Claims 1, 3 and 21 are representative of the subject matter on appeal and read as follows:

1. A protein comprising a dimer or multimer of single chain polypeptides wherein the polypeptides are non-covalently linked and each polypeptide comprises (a) a first polypeptide comprising an antigen binding portion of a variable domain of an antibody; (b) a second polypeptide comprising an antigen binding portion of a variable domain of an antibody and (c) a peptide linker linking the first and second polypeptides (a) and (b) into a single chain polypeptide having affinity for an antigen wherein the first and second polypeptide are from antibody CC49.

3. The protein of Claim 1 wherein the first polypeptide is an antigen binding portion of a light chain variable region of an antibody and the second polypeptide is an antigen binding portion of a heavy chain variable region of an antibody.

21. A method for producing a dimer or multimer of single chain polypeptides wherein the polypeptides are non-covalently linked and each polypeptide comprises (a) a first polypeptide comprising an antigen binding portion of a variable domain of an antibody; (b) a second polypeptide comprising an antigen binding portion of a variable domain of an antibody and (c) a peptide linker linking the first and second polypeptides (a) and (b) into a single chain polypeptide wherein the first and second polypeptide are from antibody CC49, the method comprising:

(I) providing a genetic sequence coding for a single chain polypeptide;

(ii) transforming a host cell with the genetic sequence;
(iii) expressing the genetic sequence in the host cell; and
(iv) recovery of single chain polypeptides which have non-covalently linked to form dimers and multimers.

The references relied on by the examiner are:

PCT Application (Huston) WO 88/09344 Dec. 1, 1988

Colcher et al. (Colcher), "In Vivo Tumor Targeting of a Recombinant Single-Chain Antigen-Binding Protein," Journal of the National Cancer Institute, Vol. 82, No. 14, pp. 1191-1197 (1990).

Rodwell et al. (Rodwell), "Linker Technology: Antibody-Mediated Delivery Systems," Biotechnology, Vol. 3, pp. 889-894 (1985).

Sheer et al. (Sheer), "Purification and Composition of the Human Tumor-Associated Glycoprotein (TAG-72) Defined by Monoclonal Antibodies CC49 and B72.3," Cancer Research, Vol. 48, pp. 6811-6818 (1988).

Pantoliano et al. (Pantoliano), "Conformational Stability, Folding, and Ligand-Binding Affinity of Single-Chain Fv Immunoglobulin Fragments Expressed in *Escherichia coli*," Biochemistry, Vol. 30, pp. 10117-10125 (1991).

All of the claims stand rejected under 35 U.S.C. § 103. In regard to claims 1, 3, 4, 8 through 18, 21 and 23, the examiner relies on Huston, Colcher, Rodwell and Sheer as evidence of obviousness. In regard to claims 24 and 25, the examiner relies on Huston, Sheer and Pantoliano. We reverse.

DISCUSSION

Claim 1, directed to a dimer or multimer of single chain polypeptides, represents the invention in its broadest aspect; each single chain polypeptide comprises two antigen binding portions from the variable domains of monoclonal antibody CC49 linked through a peptide linker, and each dimer or multimer comprises non-covalently linked single chain polypeptides. Claim 3 depends from claim 1 and specifies that each single chain polypeptide comprises an antigen binding portion from the light chain variable domain of CC49 linked to an antigen binding portion from the heavy chain variable domain of CC49. Claim 21 is directed to a method of making a dimer or multimer corresponding to that of claim 1.

There are two rejections under 35 U.S.C. § 103; Huston is the primary reference in each. We will discuss the rejections together because we view the interpretation of Huston as dispositive of the issues raised by this appeal, and we agree with appellants that "a misunderstanding has occurred with respect to [this] reference" (Brief, page 7).

According to the examiner, Huston teaches "the production of dimeric single chain antibody fragments which are non-covalently dimerized, wherein the individual heavy and light chains are linked through a peptide linker" (Examiner's Answer, page 4, emphasis added). Huston discloses a polypeptide called a biosynthetic antibody binding site (BABS). We agree with the examiner that Huston's BABS, like appellants' single chain

polypeptide, is a "single chain antibody fragment[]" in which "the individual heavy and light chains are linked through a peptide linker" (Examiner's Answer, page 4). As explained at page 7 of Huston:

> The structure of these synthetic polypeptides is unlike that of naturally occurring antibodies, fragments thereof, e.g., Fv, or known synthetic polypeptides or "chimeric antibodies" in that the regions of the BABS responsible for specificity and affinity of binding, (analogous to native antibody variable regions) are linked by peptide bonds, expressed from a single DNA . . . The polypeptides . . . comprise structures patterned after regions of native antibodies known to be responsible for antigen recognition.

The claimed invention, however, is a non-covalently linked dimer or multimer of single chain polypeptides (or BABSs, to use Huston's terminology). We have carefully reviewed the Huston reference, especially pages 21, 22, 24, 63 through 66, and figures 1B and 2B (cited by the examiner), but can find no disclosure consistent with non-covalent linkage between two or more BABSs. The only non-covalent association mentioned in the reference is <u>within</u> an individual BABS. For example, Huston states on pages 21 through 24 (references to figures omitted):

> As is now well known, Fv, the minimum antibody fragment which contains a complete antigen recognition and binding site, consists of a dimer of one heavy and one light chain variable domain in noncovalent association.
> * * *
> The structure of these biosynthetic proteins in the region which impart the binding properties to the protein is analogous to the Fv region of a natural antibody. It comprises at least one, and preferably two domains consisting of amino acids defining V_H and V_L-like polypeptide segments connected by a linker which together form the tertiary molecular structure responsible for affinity and specificity.
> * * *

> The invention thus can provide intact biosynthetic antibody binding sites analogous to V_H-V_L dimers, either non-covalently associated, disulfide bonded, or preferably linked by a polypeptide sequence to form a composite V_H-V_L or V_L-V_H polypeptide . . . The invention also provides proteins analogous to an independent V_H or V_L domain, or dimers thereof.

Further, on page 26 (references to figures omitted), Huston teaches that:

> The linker 12 should be long enough . . . to permit the chains to assume their proper conformation . . . [T]he linker may comprise an amino acid sequence patterned after a hinge region of an immunoglobulin . . . The linker may also include one or two built in cleavage sites . . . This strategy permits the V_H and V_L-like domains to be separated after expression, or the linker to be excised after folding while retaining the binding site structure in non-covalent association.

On page 28, Huston discloses a linked pair of BABS, i.e., a dimer of single chain polypeptides. We cannot agree with the examiner's conclusion that these are "dimeric single chain antibody fragments which are non-covalently dimerized" (Examiner's Answer, page 4, emphasis added). The BABS are linked through a spacer, which "may be an amino acid sequence analogous to the linker sequence [ ] or it may take other forms." According to Huston, "the spacer's primary function is to separate the active protein regions to promote their independent bioactivity and permit each region to assume its bioactive conformation independent of interference from its neighboring structure" (page 28). This does not describe the non-covalent linkage between individual single chain polypeptides required by the claims on appeal.

This deficiency in the primary reference is not remedied by any of the secondary references. In our judgment, the combined disclosures of the cited references are not

sufficient to support a conclusion of obviousness of claims requiring non-covalent linkage between single chain polypeptides. Nor are we persuaded by the examiner's comments in response to appellants' arguments. According to the examiner, "even if Huston did not suggest noncovalent dimers . . . , there is no evidence on the record that a non-covalent Fv dimer behaves any differently than a covalently bonded dimer and is therefore, considered to be an obvious variant of the covalently bonded Fv dimers" (Examiner's Answer, page 8). This is tantamount to requiring a showing of unexpected results without having established a prima facie case of obviousness in the first instance.

Both rejections of the claims under 35 U.S.C. § 103 are reversed.

REVERSED

Sherman D. Winters	)
Administrative Patent Judge	)
	)
	)
	) BOARD OF PATENT
Douglas W. Robinson	)
Administrative Patent Judge	) APPEALS AND
	)
	) INTERFERENCES
	)
Toni R. Scheiner	)
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